BIOLOGY

Guillain-Barré syndrome

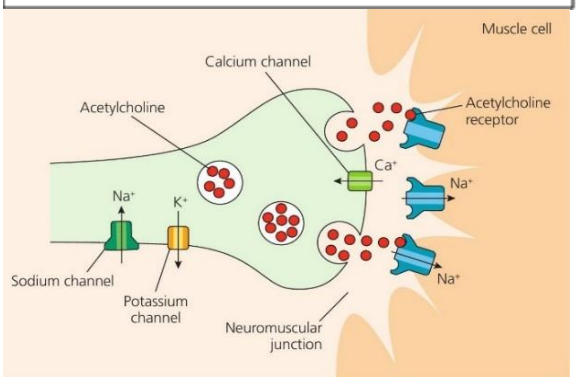
From food poisoning to paralysis

Guillain-Barré syndrome affects the peripheral neurones. It often starts with a tingling in the hands and feet, but can spread, causing paralysis of arm and leg muscles and the muscles that control breathing. In rare cases it can be fatal. Neurobiologist Maddy Cunningham explains how the syndrome can be triggered by food poisoning

Little was known about the pathological mechanisms of Guillain-Barré syndrome (GBS) until the early 1990s, when an unusual observation was made in rural China. Every summer many children would be hospitalised with breathing difficulties, a phenomenon that had not been associated with GBS. These children often had to be hand-ventilated day and night by family members to keep them alive until they recovered. Research revealed that the paralysis was brought on by an autoimmune cross-reaction.

In the hot summer months, the children were playing in rivers downstream of chicken farms. Farm waste runoff was being flushed into the river. The children had contracted food poisoning from the contaminated water and their immune systems were fighting not only the bacteria, but also their own peripheral nervous systems. Thanks to studies in patients and animal models, much more is now known about the disease.

Figure 1.1 A healthy neuromuscular junction. When an action potential reaches the terminal of the motor neurone, it triggers the release of acetylcholine from vesicles. Acetylcholine travels across the synaptic cleft to reach receptors on the muscle cell, causing contraction



To understand GBS, we need to appreciate the importance of a normally functioning peripheral nervous system. Neuromuscular junctions are the synaptic connection between the terminal end of a motor neurone and muscles. They are the sites where action potential are transmitted from nerve to muscle. They ensure that the signals from the brain are communicated to the muscles that control movement. Peripheral nerves contain axons that are extensions of the lower motor neurones. The cell bodies of these neurones are in the spinal cord, which is part of the central nervous system.

It is important for the impulses sent by the brain, via the spinal cord and peripheral nerves, to reach this meeting point and allow communication with the muscles. Many conditions can interrupt the impulses at any stage along the pathway (e.g. spinal cord injury), but many affect the neuromuscular junction (see Box 1).

Box 1 Neuromuscular junctions

A neuromuscular junction comprises two main components (see Figure 1.1). Presynaptically is the motor neurone terminal, the portion of the axon with vesicles containing the neurotransmitter acetylcholine. Postsynaptically is the muscle cell, which contains acetylcholine receptors.

In addition to these components, between the motor neurone terminal and the muscle cell is the synaptic cleft, the distance that neurotransmitters cross from neurone membrane to muscle cell membrane. When an action potential travelling along a healthy motor neurone reaches the cell terminal, its surface membrane depolarises. This allows calcium ions to enter the terminal through voltage-gated calcium ion channels, triggering the release of acetylcholine from the vesicles into the synaptic cleft. Released acetylcholine binds to acetylcholine receptors on the surface membrane of the muscle cell. These receptors are also ion channels, and their activation allows influx of Na^+ into the muscle cell, causing depolarisation of its surface membrane, leading to muscle contraction.

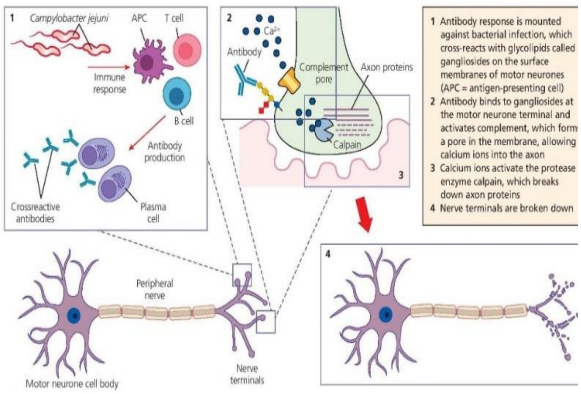
A neuromuscular junction is a vulnerable site. It is not protected by the blood-nerve barrier that surrounds the CNS, leaving it exposed to substances circulating in the blood. This allows toxins and viruses to exploit this vulnerability, as they can enter the nervous system by latching onto the terminal membrane of a motor neurone, where they are taken up by endocytosis. Botulinum toxin, for example, enters via a motor neurone terminal membrane and inhibits neurotransmitter release, preventing impulse transmission across the synaptic cleft to the muscle, resulting in muscular paralysis.
As well as circulating factors that come from outside the body, a neuromuscular junction is vulnerable to autoimmune attack by circulating antibodies generated by the body itself. You may have heard of myasthenia gravis, in which antibodies destroy acetylcholine receptors on the postsynaptic muscle cell membrane, preventing the depolarisation and activation of muscle cells. In GBS, it is the presynaptic motor neurone terminal that is affected by autoimmune antibody attack.

Autoimmunity in GBS

Even before the mysterious seasonal GBS in rural China, it was known that a recent infection often precedes the onset of GBS. However, it was with the studies of the paralysed children that the mechanism came to be more fully understood.

Many bacteria and viruses have been linked to cases of GBS. Most commonly this is *Campylobacter jejuni,* a bacterium responsible for food poisoning. These bacteria are covered by glycolipids (sugar structures with lipid tails) called **lipooligosaccharides,** which share a striking structural similarity to glycolipids called **gangliosides,** which cover our neurones. In GBS patients the immune system mounts an adaptive antibody response against the infective pathogen. However, the adaptive antibodies also cross-react with gangliosides on the surface membranes of motor neurones (see Figure 1).

Figure 1 Causes of pathology in GBS



Not everyone who gets food poisoning will suffer from GBS. From early stages in development, the body's immune system can recognise the antigens on the body's own cells, and any immune cell that could potentially react with a 'self' cell is deleted. This is called immune tolerance.

The immune system is 'tolerant' of the body's own cells and does not usually attack 'self ' cells. This is how many pathogens avoid detection by immune cells, like a 'wolf dressed in sheep's clothing' to avoid the shepherd. In patients with GBS this tolerance is broken, for reasons currently unknown, allowing the production of dangerously cross-reactive antibodies

Complement

Antibodies cause damage to nerves in GBS by activating the classical **complement** cascade, part of the innate (or passive) immune system. This is a series of enzymatic reactions, triggered when an antibody binds to its antigen, which results in the formation of a pore in the cell membrane of the pathogen. This pore results in cell lysis of the pathogen as a huge influx of extracellular fluid and ions occurs. In GBS patients, pores also form on the cell membranes of their peripheral neurones, particularly the vulnerable presynaptic motor nerve terminals of the neuromuscular junction.

The pores allow free movement of ions, which are usually kept in homeostatic balance, in and out of the axon. Crucially, this includes calcium ions, which are usually tightly regulated by calcium ion channels, that enable proper functioning of the neuromuscular junction. This huge calcium ion influx through the complement pore results in an uncontrolled release of acetylcholine from all the vesicles in the presynaptic neurone, creating uncoordinated activation of the muscles.

Since the membrane is full of complement pores, no endocytosis can occur so the vesicles cannot reform and therefore no further impulses can be transmitted to the muscles. Importantly, this unchecked calcium ion influx also acts as an 'on' switch for a protease enzyme known as **calpain,** which digests axon proteins, including those of neurofilaments (critical components of axons). All of this results in the destruction of the motor neurone terminals and paralysis of the muscles they innervate. Calcium ions are therefore an important trigger of the injury in GBS.

The future

These studies have allowed us to figure out the mechanisms of injury in GBS and identify the complement pathway as a potential target for therapeutics. The University of Glasgow and Greater Glasgow and Clyde NHS trust collaborated on the first worldwide trial of complement inhibition in GBS in 2016, with promising results. Since then, other trials have taken place worldwide with various inhibitors of the complement pathway. The goal is that patients will be able to recover their normal muscle function faster and more efficiently by more rapidly restoring the connections between their neurone terminals and muscles.